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Abstract: The aim of this study was to evaluate the effects of pheniramine and diphenhydramine, two histamine H1 receptor antagonists, on spinal anesthesia and their comparison with lidocaine, a commonly used local anesthetic. After rats were injected intrathecally with diphenhydramine and pheniramine, the dose—response curves were obtained. The potency and duration of diphenhydramine and pheniramine on spinal anesthesia were compared with lidocaine. We showed that diphenhydramine and pheniramine produced dose-dependent spinal blockades in motor function, proprioception, and nociception. On a 50% effective dose (ED50) basis, the rank of potency of drugs was diphenhydramine = pheniramine > lidocaine ($p < 0.05$ for the differences). In equianesthetic doses (ED25, ED50, and ED75), the block duration caused by diphenhydramine was longer than that caused by pheniramine or lidocaine ($p < 0.01$ for the differences). Diphenhydramine, but not pheniramine or lidocaine, elicited longer duration of sensory block than that of motor block at the same dose of 1.75 μmol. These preclinical data reported that diphenhydramine with a more sensory-selective action over motor blockade demonstrated more potent and longer-lasting spinal blockades, compared with pheniramine or lidocaine.

Spinal anesthesia with diphenhydramine and pheniramine in rats

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ABSTRACT

The aim of this study was to evaluate the effects of pheniramine and diphenhydramine, two histamine H_1 receptor antagonists, on spinal anesthesia and their comparison with lidocaine, a commonly used local anesthetic. After rats were injected intrathecally with diphenhydramine and pheniramine, the dose—response curves were obtained. The potency and duration of diphenhydramine and pheniramine on spinal anesthesia were compared with lidocaine. We showed that diphenhydramine and pheniramine produced dose-dependent spinal blockades in motor function, proprioception, and nociception. On a 50% effective dose (ED_{50}) basis, the rank of potency of drugs was diphenhydramine = pheniramine > lidocaine ($p < 0.05$ for the differences). In equianesthetic doses (ED_{25}, ED_{50}, and ED_{75}), the block duration caused by diphenhydramine was longer than that caused by pheniramine or lidocaine ($p < 0.01$ for the differences). Diphenhydramine, but not pheniramine or lidocaine, elicited longer duration of sensory block than that of motor block at the same dose of 1.75 μmol. These preclinical data reported that diphenhydramine with a more sensory-selective action over motor blockade demonstrated more potent and longer-lasting spinal blockades, compared with pheniramine or lidocaine.

1. Introduction

Diphenhydramine and pheniramine, two histamine H_1 receptor antagonists, are widely used antihistaminics (Estelle and Simons, 1999; Pullman et al., 1975; Sharma and Hamelin, 2003) and have antipruritic effects (Pavlidakey et al., 2009). Diphenhydramine is a first generation antihistamine mainly used to treat allergies and may act as an antiemetic, sedative and hypnotic (Pavlidakey et al., 2009; Shepherd, 2011). Diphenhydramine also has the local anesthetic properties (Steffen et al., 1956), and has been used successfully as a local cutaneous anesthetic when allergies to other local anesthetic agents exist (Pollack and Swindle, 1989). From that time onwards, there is a growing body of evidence that diphenhydramine had topical ocular and dermal local anesthetic properties (Green et al., 1994; Pavlidakey et al., 2009; Suffridge et al., 2009).

Diphenhydramine has been shown to have the characteristic of the blockade of Na^+ currents (Kim et al., 2000; Kuo et al., 2000), which is one of the major mechanisms of local anesthesia, produces spinal anesthesia, peripheral nerve block, and infiltrative cutaneous analgesia (McLure and Rubin, 2005). However, to the best of our knowledge, no study of diphenhydramine or pheniramine on spinal anesthesia has been reported to date. Spinal anesthesia is a relatively simple technique, which brings competent surgical conditions by the injection of a small amount of local

anesthetic with easy landmarks, giving a wide popularity to this practice

(Vandermeersch et al., 1991). The aim of this study was to evaluate the spinal

anesthesia following intrathecal injections of diphenhydramine and pheniramine by

testing motor function, proprioception, and nociception on rats. Lidocaine, a known

local anesthetic, was used as control.

2. Materials and methods

2.1. Animals

The experiment was approved by the Institutional Animal Care and Use

Committee of China Medical University, Taiwan on 11 January 2010 and conformed

to the recommendations and policies of the International Association for the Study of

Pain (IASP). Two hundred and sixteen male Sprague-Dawley rats weighting

300-350g were obtained from the National Laboratory Animal Centre in Taiwan, and

then housed in a climate controlled room maintained at 21℃ with approximately 50%

relative humidity. Lighting was on a 12-h light/dark cycle (light on at 6:00 AM), with

food and water available *ad libitum* up to time of the experiment.

2.2. Drugs

Diphenhydramine HCl, pheniramine maleate, and lidocaine HCl monohydrate

were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All drugs

in stock were freshly prepared in 5% dextrose as solution before intrathecal injections.

After injections, the low pH of these plain solutions (range, 6.0–6.5) is likely to be

buffered quickly by the cerebral spinal fluid (pH 7.4).

2.3. Experimental protocols

Three specific experiments were carried out. In experiment 1, the effects of

diphenhydramine (0.30, 0.60, 0.90, 1.50, 1.75 μmol), pheniramine (0.40, 0.75, 0.90,

1.50, 1.90 µmol), lidocaine (0.50, 0.75, 1.00, 1.50, 2.50 µmol), and vehicle (5%

dextrose) on spinal block were evaluated (n=8 rats for each dose of each drug). In

experiment 2, the spinal block effect of diphenhydramine or pheniramine was

compared with that of lidocaine at the same dose of 1.75 µmol (n=8 rats for each dose

of each drug). In experiment 3, on an equipotent basis (ED_{25}, ED_{50} and ED_{75}), the

duration of lidocaine on spinal anesthesia was compared with that of

diphenhydramine or pheniramine (n=8 rats for each dose of each drug).

2.4. *Spinal anesthesia by intrathecal injections of drugs*

All animals were injected intrathecally one time in this study. Lumbar puncture

was done on conscious rats. Before the intrathecal injections, local anesthesia was

given. Following an optimal flexion of the rat lumbar spine under prone position, each

50-µl of 0.5% lidocaine was injected into the right- and left- side of paraspinal space

(0.5 cm in depth) which was 0.5 cm away from the mid-point of the longitudinal line

of L4–5 intervertebral space (Chen et al., 2010b; Leung et al., 2010). Two minutes

later, a 27-gauge needle attached to a 50-µl syringe (Hamilton, Reno, Nevada) was

inserted into the mid-line of the L4–5 intervertebral space until a tail-flick indicated

entrance into the intrathecal space. Fifty microliters of drug were injected and the rat

was observed for the development of spinal blockade, indicated by paralysis of both

hind limbs. Rats, which demonstrated unilateral blockade, were excluded from the

study and sacrificed by using an over dose of isoflurane.

2.5. *Neurobehavioral evaluation*

After intrathecal injection of drug, three neurobehavioral evaluations, which

consisted of evaluations of motor, proprioception, and nociception, were conducted

(Chen et al., 2007; Chen et al., 2010a). For consistency, a trained examiner who was

blinded to the treatment groups was responsible for handling of all animals and

behavioral examinations. Rats were evaluated before medication and at 1, 5, and 10

min afterwards, then again at 10-min interval until 1 h and at 15 min interval until 2 h.

The magnitude of spinal blockade in motor function, proprioception, and nociception

was described as the percentage of possible effect (% PE). The maximum blockade in

a time course of spinal anesthesia of drugs was described as the percent of maximal

possible effect (% MPE).

In brief, nociception was evaluated by the withdrawal reflex elicited by pinching

a skin fold over each rat's back at 1 cm from the proximal part of the tail, the lateral

metatarsus of bilateral hind limbs, and the dorsal part of the mid-tail. At each testing

time, only one pinch was given to each of the four testing sites, and the time interval

between stimulations at different sites was around 2 s. The nociceptive blockade was

graded as 4 (normal or 0% MPE), 3 (25% MPE), 2 (50% MPE), 1 (75% MPE), and 0

(absent or 100% MPE) (Chen et al., 2004; Hung et al., 2009).

Proprioception evaluation was based on the resting posture and postural reactions ('tactile placing' and 'hopping'). This test was performed by lifting the front half of the animal off the ground and lifting one hind limb at a time off the ground so that the animal was standing on just one limb. Then, the animal was moved laterally, which normally evoked a prompt hopping response with the weight-bearing limb in the direction of movement to prevent the animal from falling. A predominantly proprioceptive block causes a delayed hopping followed by greater lateral hops to prevent the animal from falling. The functional deficit was graded as 3 (normal or 0% MPE), 2 (slightly impaired), 1 (severely impaired), and 0 (completely impaired or 100% MPE) (Chen et al., 2004; Hung et al., 2009).

Motor function was evaluated by measuring 'the extensor postural thrust' of the right hind limb of each rat. The extensor thrust was measured as the gram force, which resisted contacting the platform by the rat heel applied to a digital platform balance (Mettler Toledo, PB 1502-S, Switzerland). The reduction in this force, representing reduced extensor muscle tone, was considered as a deficit of motor function and expressed as a percentage of the control force. The preinjection control value was considered as 0% motor block or 0% maximal possible effect (% MPE). A force less than 20 g (also referred to as the weight of the 'flaccid limb') was interpreted as the absence of extensor postural thrust or a 100% motor block or 100%

MPE (Leung et al., 2010; Thalhammer et al., 1995).

2.6. Effective doses (EDs)

After intrathecally injecting the rats with four different doses of each drug (n = 8 for each dose of each drug), the dose—response curve was constructed. The curve was then fitted using a SAS Nonlinear (NLIN) Procedures (SAS Institute Inc., Carey, NC), and the value of 50% effective dose (ED_{50}), defined as the dose that caused 50% spinal anesthesia, were obtained (Chen et al., 2011a; Minkin and Kundhal, 1999). The ED_{25} or ED_{75} of drug was obtained by the same curve-fitting (SAS NLIN Procedures) which was used to derive the ED_{50} (Chen et al., 2011b; Minkin and Kundhal, 1999). The full recovery time, defined as the interval from injection to full recovery, caused by each drug (n = 8 rats for each dose of each drug) was evaluated on an equipotent basis (ED_{25}, ED_{50} and ED_{75}). In this study, we also evaluated the %MPE, complete blockade time, time to full recovery, area under curves (AUCs) of motor, proprioception and nociception for diphenhydramine, pheniramine, and lidocaine at the same dose of 1.75 μmol. The AUC of spinal blockade of drug was obtained by using Kinetica v 2.0.1 (MicroPharm International, USA).

2.7. Statistical analysis

Data are presented as means ± S.E.M. or ED_{50} values with 95% confidence interval (95% CI). Values were evaluated by either 1-way (experiments 1 and 2) or

2-way (experiment 3) analysis of variance (ANOVA) followed by pairwise Tukey's

honest significance difference (HSD) test. A statistical software, SPSS for Windows

(version 17.0, SPSS, Inc, Chicago, IL, USA), was used, and a P value less than 0.05

was considered statistically significant.

3. Results

3.1. *The spinal blockade of diphenhydramine and pheniramine*

Diphenhydramine and pheniramine, as well as lidocaine, displayed dose-dependent effects on spinal anesthesia in rats (Fig. 1). Intrathecal injection of 5% dextrose (vehicle) produced no spinal anesthetic effects (data not shown). The ED_{50}s of drugs are shown in Table 1. On the ED_{50} basis, the ranks of potencies in motor function, proprioception, and nociception were diphenhydramine = pheniramine > lidocaine ($P < 0.05$; Table 1). Furthermore, the sensory/nociceptive blockade (ED_{50}) was more potent than the motor blockade for diphenhydramine, but not lidocaine or pheniramine ($P < 0.05$; Table 1).

3.2. *The spinal blockade of diphenhydramine, pheniramine, and lidocaine at the dose of 1.75 μmol*

At a given dose of 1.75 μmol, diphenhydramine showed 100, 100, and 100% of blockades (% MPE) in motor function, proprioception, and nociception with duration of action of about 41, 56, and 88 min, respectively (Fig. 2). Pheniramine at 1.75 μmol demonstrated 94, 92, and 94% of blockades in motor function, proprioception, and nociception with duration of action of about 25, 28, and 35 min, respectively. At the same given dose, lidocaine displayed 74, 75, and 81% of blockades in motor function, proprioception, and nociception with duration of action of about 19, 19, and 23 min,

respectively (Fig. 2 and Table 2). Of note, diphenhydramine at 1.75 μmol elicited complete spinal blockade (100% MPE) of motor function, proprioception, and nociception (Fig. 2 and Table 2).

3.3. *The complete block time, full recovery time, and AUCs of diphenhydramine, pheniramine, and lidocaine on spinal anesthesia*

The complete block time, time to full recovery, and AUCs of spinal anesthesia of diphenhydramine are significantly greater than those of pheniramine or lidocaine in Figure 2 and Table 2. In addition, diphenhydramine also elicited longer duration of sensory blockade than that of motor blockade (Table 2). On an equipotent basis (ED$_{25}$, ED$_{50}$, and ED$_{75}$), all drugs tested produced similar duration in motor blockades, but the blockades of proprioception and nociception caused by diphenhydramine were longer than those caused by pheniramine or lidocaine (Fig. 3).

4. Discussion

We reported that diphenhydramine and pheniramine produced dose-dependent

spinal anesthesia in rats. Diphenhydramine was more potent at producing spinal

blockades than pheniramine or lidocaine. At equianesthetic doses, diphenhydramine

displayed the longest duration of action of sensory/nociceptive block among these

three drugs.

In this study, diphenhydramine and pheniramine blocked motor, sensory, and

proprioceptive functions, suggesting the spinal (local) anesthetic characteristics of

diphenhydramine and pheniramine. It has been known that local anesthetics produce

neural blockade by inhibiting the sodium currents in the nervous tissues through the

voltage-gated sodium channels (McLure and Rubin, 2005). Because diphenhydramine

blocked sodium channels (Kim et al., 2000; Kuo et al., 2000), it produced dermal

local anesthesia (Green et al., 1994), topical anesthesia (Suffridge et al., 2009), and

spinal anesthesia. Although the pharmacology of pheniramine is largely unknown, our

study showed that pheniramine produced a dose-dependent spinal anesthetic effect.

We showed that diphenhydramine, pheniramine, and lidocaine produced

dose-dependent spinal anesthesia. Diphenhydramine produced almost 1.1- and

1.4-folds higher potency than did pheniramine or lidocaine on spinal anesthesia,

respectively. Our results are in agreement with that previous injection of lesser

diphenhydramine (20mg) dose with venous occlusion can be considered as an

alternative to larger lidocaine (40mg) dose in decreasing the prevalence of pain

caused by injection of propofol into forearm veins (Apiliogullari et al., 2007).

Antihistamines are easily available medications. On an equal mole basis (1.75

μmol), spinal block duration of diphenhydramine was longer than that of pheniramine

or lidocaine (Fig. 2 and Table 2). Among these three drugs, diphenhydramine elicited

predominantly nociceptive-specific blockades. In addition, diphenhydramine

produced a longer duration of sensory blockade than the motor blockade (Fig. 2 and

Fig. 3). Furthermore, we found that the nociceptive blockade (ED_{50}) was more potent

than the motor blockade (ED_{50}) for diphenhydramine, but not pheniramine or

lidocaine. The sensory/nociceptive blockade in diphenhydramine was almost 1.2-folds

higher potency (ED_{50}) than the motor blockade. Clinically, local anesthetics have

mostly been used to assist with complete blockage of pain and not to augment

potency.

Surgery by injecting long-acting local anesthetics is frequently practiced (Job et

al., 1979). There are few cases where ultrashort spinal anesthesia is needed, and for

these they use 2-chloroprocaine, lidocaine or mepivacaine clinically. For this reason,

we evaluated diphenhydramine, pheniramine, and lidocaine at equianesthetic doses

(ED_{25}, ED_{50}, and ED_{75}). Our results demonstrated that the duration of spinal blockade

caused by diphenhydramine was longer than that caused by pheniramine or lidocaine

on an equipotent basis (Fig. 3). Treatment with local anesthetics (e.g.

diphenhydramine) for surgery or postoperative pain control may be worth studied in

the future.

Our study has some limitations. We did not evaluate whether

diphenhydramine and pheniramine had neurotoxicity, however, it is noteworthy that

in neurobehavioral studies we detected no apparent side effects after drug injection.

Although we used diphenhydramine at 1.75 µmol (1.0%) to elicit complete spinal

block, Suffridge et al. have proved that all 5% diphenhydramine-treated eyes showed

no toxic effects on the corneal epithelium on New Zealand rabbits (Suffridge et al.,

2009). Histologic studies must be performed in the future before the possible use of

diphenhydramine and pheniramine as spinal analgesic in humans.

In conclusion, the preclinical data reported that diphenhydramine and

pheniramine elicited local anesthetic effects on spinal anesthesia in rats.

Diphenhydramine with a more sensory-selective action over motor blockade is more

potent and longer spinal block duration than pheniramine or lidocaine. The neural

block potential by diphenhydramine and pheniramine is worth studying in the further.

Acknowledgements

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Table 1. The 50% effective doses (ED_{50}s) of drugs on spinal anesthesia in rats

	ED$_{50}$ (95% CI)			Mean		
	Motor	Proprioception	Nociception	ED$_{25}$	ED$_{50}$	ED$_{75}$
Diphenhydramine	0.99 (0.91–1.10)	0.82 (0.73–0.92)	0.80 (0.73–0.88)	0.62	0.86	1.23
Pheniramine	1.07 (0.97–1.14)	0.97 (0.90–1.03)	0.89 (0.82–0.97)	0.77	0.98	1.33
Lidocaine	1.30 (1.19–1.41)	1.15 (1.07–1.26)	1.06 (0.99–1.19)	0.83	1.17	1.58

ED_{50}s of drugs (μmol) were obtained from Figure 1. CI = confidence interval. The potencies of drugs (ED_{50}s) were diphenhydramine = pheniramine > lidocaine ($P<0.05$, for each comparison) by using 1-way ANOVA followed by pairwise Tukey's HSD test.

Table 2. The percent of maximal possible effect (%MPE), duration, area under curves (AUCs) of drugs on spinal anesthesia in rats

	%MPE	Duration (min)		AUCs (%MPE x min)
		Complete blockade time	Time to full recovery	
Motor				
Diphenhydramine	100 ± 0	$15 \pm 4^{\#\#}$	$41 \pm 7^{\#\#\#}$	$2022 \pm 456^{\#\#\#}$
Pheniramine	$94 \pm 4^{\dagger}$	-	$25 \pm 4^{*}$	$906 \pm 227^{*}$
Lidocaine	$74 \pm 6^{**}$	-	$19 \pm 1^{**}$	$477 \pm 53^{**}$
Proprioception				
Diphenhydramine	100 ± 0	$19 \pm 4^{\#}$	$56 \pm 7^{\#\#}$	$3421 \pm 483^{\#\#}$
Pheniramine	$92 \pm 5^{\dagger}$	-	$28 \pm 3^{***}$	$1206 \pm 249^{***}$
Lidocaine	$75 \pm 5^{**}$	-	$19 \pm 1^{***}$	$573 \pm 57^{***}$
Nociception				
Diphenhydramine	100 ± 0	43 ± 8	88 ± 5	6226 ± 502
Pheniramine	$94 \pm 4^{\dagger}$	-	$35 \pm 3^{***}$	$1707 \pm 258^{***}$
Lidocaine	$81 \pm 4^{**}$	-	$23 \pm 2^{***}$	$836 \pm 78^{***}$

Spinal anesthesia (means ± S.E.M.) with drugs at the same dose of 1.75 μmol (n = 8 in each group). Of note, all of the rats in the

diphenhydramine group demonstrated complete blockade (100%MPE) of any function tested. Symbols (*, **, ***) indicate $P < 0.05$, $P < 0.01$, $P < 0.001$ when diphenhydramine compared with pheniramine or lidocaine; The symbol (†) indicates $P < 0.05$ when pheniramine compared with lidocaine; Symbols ($^{\#}$, $^{\#\#}$, $^{\#\#\#}$) indicate $P < 0.05$, $P < 0.01$, $P < 0.001$ when nociception compared with motor or proprioception.
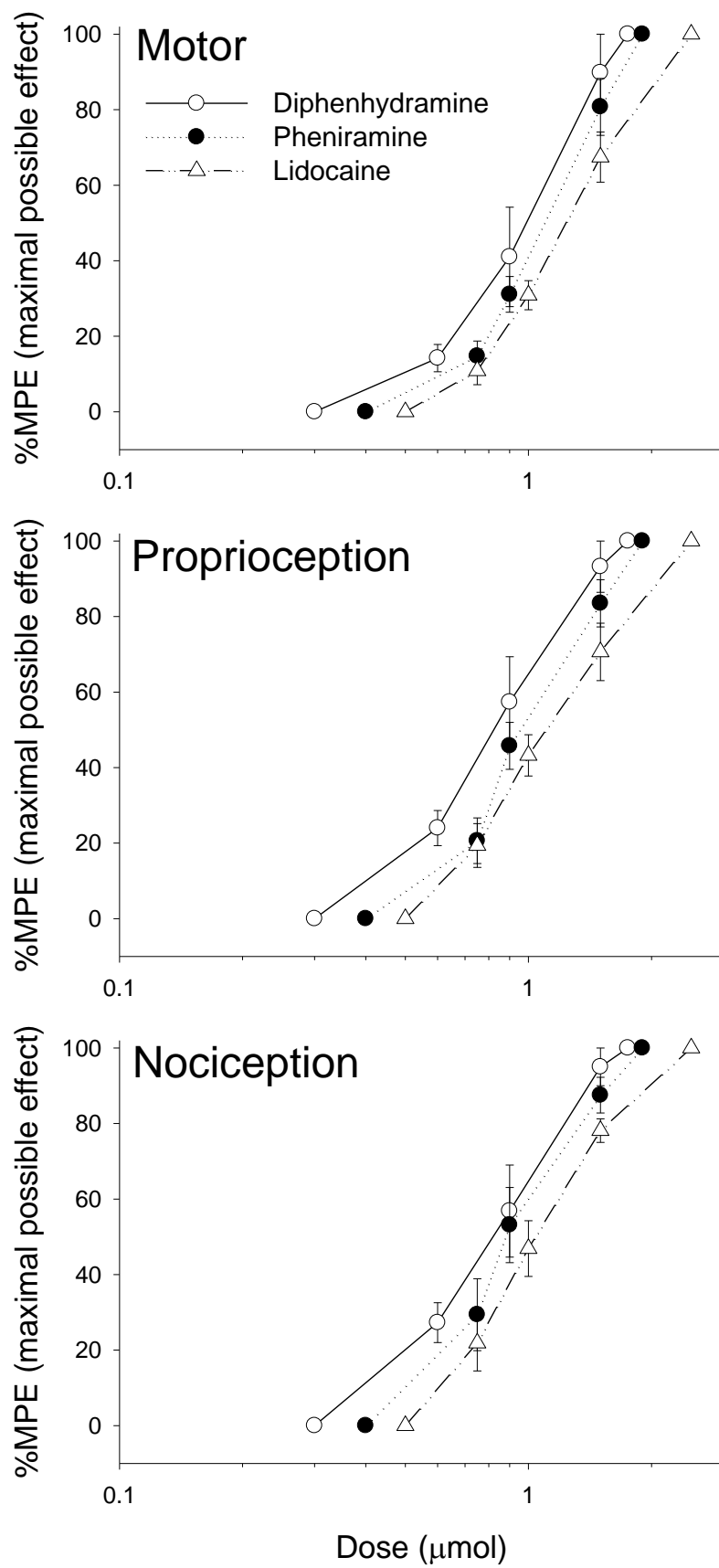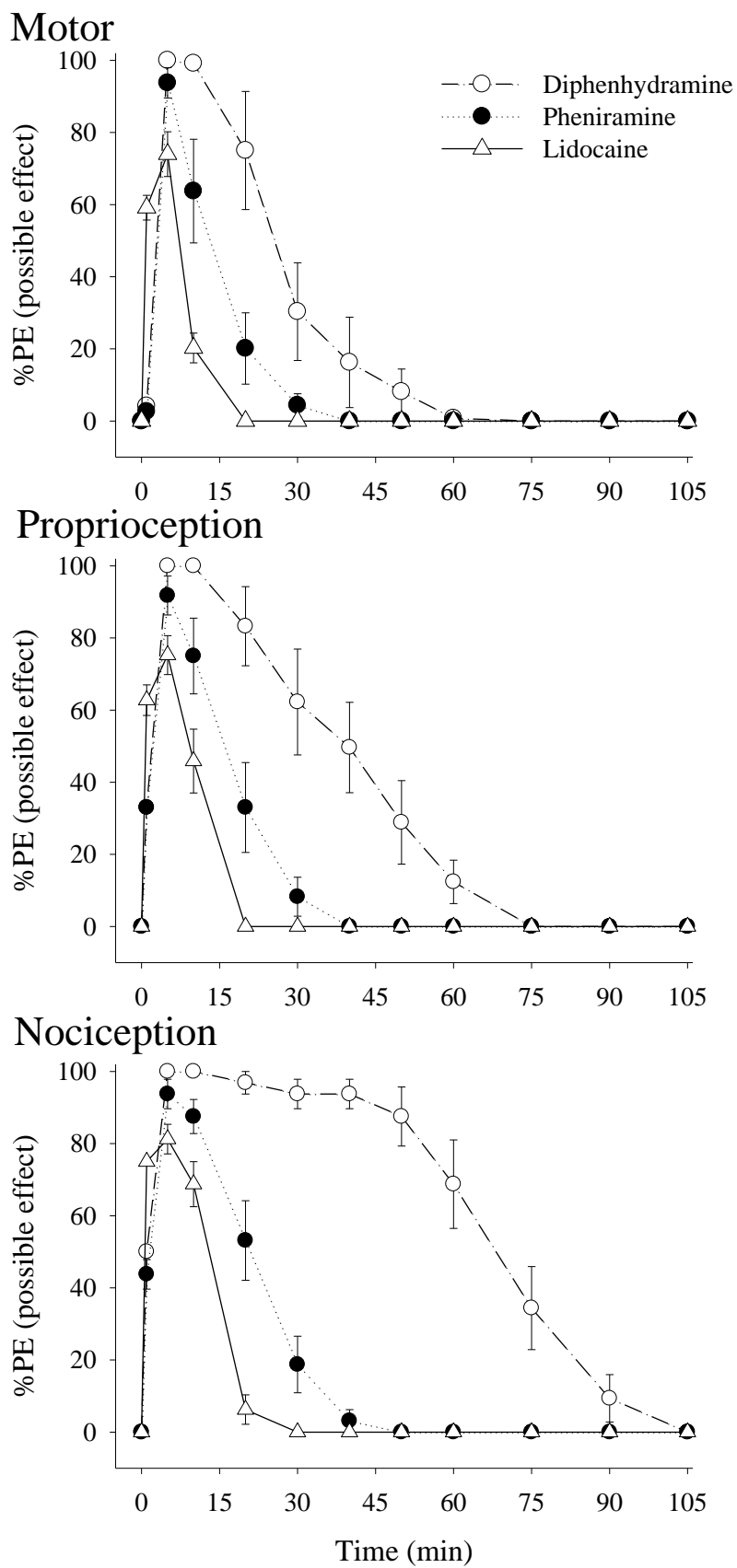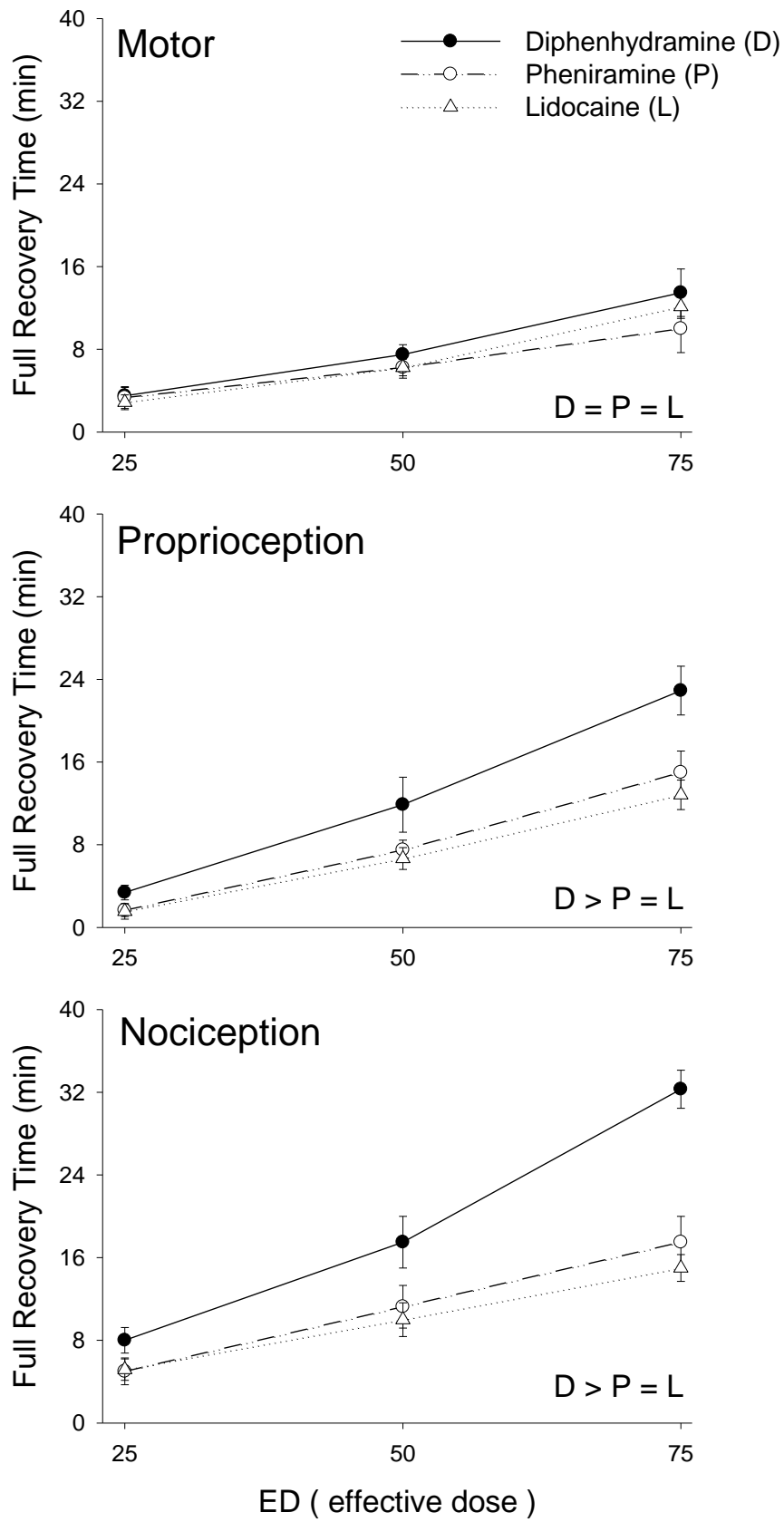
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Fig. 1.

Fig. 2.

Fig. 3.

Figure Legends

Fig. 1. The dose—response curves of diphenhydramine, pheniramine, and lidocaine on spinal blockades of motor, proprioception, and nociception (% MPE) in rats ($n = 8$ at each testing point). Data are means ± S.E.M. %MPE = percent of maximal possible effect.

Fig. 2. Time courses of diphenhydramine, pheniramine, and lidocaine on spinal anesthesia at the same dose of 1.75 μmol in rats. Values are expressed as means ± S.E.M. Each testing point of the time course study contained eight rats.

Fig. 3. Full recovery time (duration) of action of diphenhydramine, pheniramine, and lidocaine on spinal anesthesia at doses of ED_{25}, ED_{50}, and ED_{75} ($n = 8$ at each testing point). Values are expressed as means ± S.E.M.